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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| HALVORSON, MARK | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/02/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/823,254 | KIENER ET AL. | |
| | Examiner | Art Unit | |
| | Mark Halvorson | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *4/12/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *4-6 8, 15, 18-26, 29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,9-14,16,17,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/2005, 2/8/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-32 are pending.

### *Election/Restrictions*

Applicant's election of Group I in the reply filed on Feb 27, 2007 is acknowledged. Applicant's election of epithelial cell disorder, lung fibrosis, secretion of inflammatory factors, increase in EphA2 phosphorylation, one or more immunomodulatory agents, antibody, secretion of fibronectin is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 31and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 4-6 8, 15, 18-26, 29 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.
Claims 1-3, 7, 9-14, 16, 17 and 27-28 are currently under examination.

### *Specification*

The Abstract of the disclosure is objected to because it exceed the maximum length of 150 words. Correction is required. See 37 CFR §172

The disclosure is objected to because of the following informalities: There are no application numbers for three patent applications on page 57 are blank. Correction is required.

### *Claim Objections*

Claim 27 is objected to for being dependent on a non-elected claim (claim 15)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims1-3, 7, 9-14, 16, 17 and 27-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of treating a non-neoplastic hyperproliferative cell or excessive cell accumulation disorder in a patient comprising administering a therapeutically effective amount of an EphA2 agonistic agent, wherein said EphA2 agonistic agent binds EphA2, wherein said non-neoplastic hyperproliferative cell or excessive cell accumulation disorder is lung fibrosis, wherein a pathology-causing cell phenotype of said hyperproliferative epithelial cell disorder is secretion of inflammatory factors, wherein said EphA2 agent is an antibody.

The specification discloses an in vitro model of fibrosis in which transformed bronchial epithelium cell were treated with bleomycin. (page 89 lines 12-17). EphA2

protein expression was upregulated in the transformed cells 24 hours after treatment with bleomycin. (page 92, lines 15-27). The specification also discloses that treatment of breast carcinoma cells with antibodies to EphA2 in vitro resulted in tyrosine phosphorylation and degradation of EphA2. (page 85, line 30 to page 86, line 19).

Expression of EphA2 is frequently upregulated in many invasive cancers (Coffman et al Can Res, 2003, 63:7907-7912). The role of EphA2 in lung fibrosis is not known. Further, the treatment of lung fibrosis is quite unpredictable. Wang et al (Biochemical Pharmacology, 200, 60:1949-1958) states that induced pulmonary fibrosis is a crippling disease and responds poorly to current therapy Page 1955, 1st column, 2nd paragraph). Applicants acknowledge the difficulty in the treatment of fibrotic lung diseases by stating that currently that no treatments are known to be effective (page 6, lines 1-3 of the specification). Furthermore, Chua et al (Am J Respir Cell Mol Biol, 2005, 33:9-13) recently alluded to the lack of any adequate treatment for pulmonary fibrosis. (page 12 2nd column 4th paragraph). Thus, the amount of knowledge in the art concerning the successful treatment of fibrotic lung disease is low especially the treatment of fibrotic disease in vivo with antibodies. In this regard, Wang et al demonstrated that antibodies to the $\alpha^4$ integrin reduced the number of lesions in a mouse model of pulmonary fibrosis (page 1954 1st column, 2nd paragraph) compared to controls.

The claims of the instant application are not enabled because the teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. Thus, the claims are not enabled for treating a non-neoplastic hyperproliferative cell or excessive cell accumulation disorder in a patient in-vivo. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell

interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. In this regard Chua et al (Am J Respir Cell Mol Biol, 2005, 33:9-13) when discussing in vivo models for pulmonary fibrosis stated that "in vitro systems are limited to probing particular cellular or molecular responses that in isolation are too remote from actual lung pathophysiology." (page 10, 2nd column, 2nd paragraph).

In addition, the treatment of disease with antibodies in vivo is generally unpredictable. White et al (Annu Rev Med 52:125-145, 2001) discloses that despite monoclonal antibody testing since the mid-1900's only in the past three years have

some monoclonal antibodies provided sufficient efficacy as therapeutic agents (see Abstract). According to White et al, "The use of monoclonal antibodies for the treatment of carcinoma and hematologic malignancies is an evolving field". (see Conclusion). White et al discloses that numerous obstacles must be overcome for successful immunotherapy. These include choice of target antigen, immunogenicity of the antibodies, length of half-life and ability to recruit effector functions and antibody manufacturing.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

It is apparent from the art that the treatment of lung fibrosis is unpredictable. Wang et al states that induced pulmonary fibrosis is a crippling disease and responds poorly to current therapy Page 1955, 1st column, 2nd paragraph). Applicants acknowledge the difficulty in the treatment of fibrotic lung diseases by stating that currently that no treatments are known to be effective (page 6, lines 1-3 of the specification). All of this underscores the criticality of providing workable examples. However, there are no working examples for the treatment of lung fibrosis comprising administering a therapeutically effective amount of an antibody to EphA2 in vivo. The specification provides insufficient guidance with regard to these issues and provides no

working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

Additionally, claims 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim is drawn to method of treating a non-neoplastic hyperproliferative cell or excessive cell accumulation disorder in a patient comprising administering a therapeutically effective amount of an EphA2 agonistic agent, wherein said EphA2 agonistic agent binds EphA2, wherein said non-neoplastic hyperproliferative cell or excessive cell accumulation disorder is lung fibrosis, wherein a pathology-causing cell phenotype of said hyperproliferative epithelial cell disorder is secretion of inflammatory factors, wherein said EphA2 agent is an antibody, wherein the said antibody is a monoclonal antibody, wherein said monoclonal antibody is Eph099B-102.147, Eph099B-208.261, Eph099B-210.248, or B233 or comprises a CDR from Eph099B-102.147, Eph099B-208.261, Eph099B-210.248, or B233.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (PNAS, 1982, 79 page 1979). Rudikoff et al. teach that the alteration

of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1ß antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that a method of treating a lung fibrosis in a patient comprising administering a therapeutically effective amount of an antibody to will predictably function as disclosed. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims, the lack of guidance and support in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

The specification also fails to provide sufficient enablement for the claimed methods drawn to methods of using specific antibodies, Eph099B-102.147, Eph099B-208.261, Eph099B-210.248, or B233. It is not clear from the disclosure that the deposits of Eph099B-102.147, Eph099B-208.261, Eph099B-210.248, or B233 meet all the criteria set forth in MPEP 2410.02 items 1-3. Specifically,0095 on pages 25-26 of the specification fails to indicate that all restrictions on the availability to the public of the deposited antibodies will be irrevocably removed upon the granting of a patent. Assurance of compliance may be in the form of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicant's agent identifying a deposit of

biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC §122.

6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

As a means of completing the record, Applicants may submit a statement indicating that all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application

***Summary***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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